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Review

Diet-induced metabolic disturbances as modulators of brain homeostasis

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ABSTRACT

A number of metabolic disturbances occur in response to the consumption of a high fat western diet. Such metabolic disturbances can include the progressive development of hyperglycemia, hyperinsulemia, obesity, metabolic syndrome, and diabetes. Cumulatively, diet-induced disturbances in metabolism are known to promote increased morbidity and negatively impact life expectancy through a variety of mechanisms. While the impact of metabolic disturbances on the hepatic, endocrine, and cardiovascular systems is well established there remains a noticeable void in understanding the basis by which the central nervous system (CNS) becomes altered in response to diet-induced metabolic dysfunction. In particular, it remains to be fully elucidated which established features of diet-induced pathogenesis (observed in non-CNS tissues) are recapitulated in the brain, and identification as to whether the observed changes in the brain are a direct or indirect effect of peripheral metabolic disturbances. This review will focus on each of these key issues and identify some critical experimental questions which remain to be elucidated experimentally, as well as provide an outline of our current understanding for how diet-induced alterations in metabolism may impact the brain during aging and age-related diseases of the nervous system.

1. Western diet, metabolic dysfunction, and metabolic syndrome

In the last decade there has been a tremendous shift in both the composition of the daily diet as well as the basic dietary habits of Western societies, whereby a growing percentage of the population primarily consumes a diet that is high in fat, and a diet whereby an excess of calories is consumed on a regular basis. Studies as early as 1913 highlighted the relationship between the consumption of a high fat diet and the development of hyperglycemia [1], demonstrating that a high fat diet is sufficient to promote systemic metabolic disturbances. Similarly, studies have established that overfeeding or excessive caloric intake is sufficient to promote systematic metabolic disturbances in both rodents and humans [2–5]. As such it is now clear that there is a tremendous and negative impact on metabolic balance in a growing percentage of individuals in Western society as the result of both increased dietary fat and elevated caloric intake. This dietary-mediated increase in metabolic dysfunction is evident in the manifestation of the growing percentage of individuals who exhibit hyperglycemia, hyperinsulemia, insulin resistance, dyslipidemia, triglyceremia, and free fatty acid disturbances. Cumulatively, these aspects of metabolic dysfunction will undoubtedly increase morbidity and mortality in Western societies in an unprecedented manner.

The focus of this review is to provide a comprehensive and focused analysis of how dietary-induced metabolic dysfunction is capable of disrupting brain homeostasis and likely contributes to the development of brain dysfunction and brain pathogenesis. In particular this review will discuss the potential interplay between diet-induced alterations in metabolism and the resulting changes in the brain homeostasis which occur during aging and age-related diseases of the nervous system.

Before moving on to a discussion of the interplay between metabolic dysfunction and brain pathogenesis it is worth spending a moment to clarify the progressive nature by which a high fat western diet promotes systematic metabolic disturbances. This is because most of the current literature on the brain and metabolic dysfunction have focused solely on the effects of diabetes, which is one of the last and most devastating forms of metabolic dysfunction that can be induced by a western diet. Certainly diabetes is capable of promoting brain disturbances, however in addition to the irreversible state of diabetes, one must also consider the impact a pre-diabetic state may have on brain homeostasis. Currently there are believed to be 41 million Americans that can be considered to be prediabetic, with the prediabetic state is associated with a progressive development of multiple metabolic disturbances which precedes the irreversible stage of diabetes, and importantly can even occur independent of the development of diabetes [2–8]. The specific clinical endpoints that are most commonly utilized to identify prediabetic individuals include the presence of an impaired fasting glucose (IFG) and an impaired glucose tolerance (IGT) test. Biochemically, these diet-induced disturbances in metabolism commonly occur in a progressive and somewhat systematic manner (Fig 1). One of the earliest metabolic disturbances which is known to occur in the development of dietary induced diabetes is an increase in the flux of free fatty acids (FFA) into

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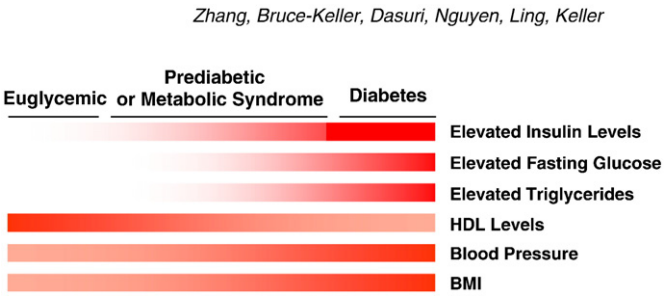

Fig. 1. Progression from euglycemic state to diabetes. In contrast to the a healthy euglycemic state, the consumption of a western diet is sufficient to increase the dysfunction of a number of aspects of metabolism. The temporal profile by which many on these metabolic disturbances occur is provided to allow for identification of early and late events in the progression to diabetes. HDL: high density lipoprotein; BMI: body mass index.

a variety of tissues (liver, pancreas, muscle), which is subsequently followed by the deposition of triglycerides into these same tissues (Fig 1). Elevations in FFA are believed to promote metabolic disturbances in part by impairing the ability of cells to store glucose and to respond to insulin, which cumulatively (according to the Randle hypothesis) are capable of promoting the development of diabetes. Accompanying each of these alterations there is observed to be an elevation in circulating levels of cytokines, altered levels of specific adipose derived factors (termed adipokines), and further sustained elevations in FFA levels (Fig 1). Cumulatively, these events lead to elevated levels circulating insulin (hyperinsulemia), whereby the body attempts to overcome the impairment of downstream insulin signaling by sustaining higher and higher levels of circulating insulin (Fig 1). Allowed to persist these conditions give rise to continually elevated levels of glucose (due to impaired insulin-mediated regulation of glucose levels) and can promote pancreatic beta cell damage to the point that an irreversible state of metabolic dysfunction occurs (i.e. -diabetes) (Fig 1).

In addition to the identification of a pre-diabetic state, studies have now established a clinical phenotype referred to as metabolic syndrome [9–11]. Metabolic syndrome is clinically defined by the presence of up to 5 different cardiovascular risk factors. These factors are the presence of abdominal obesity, low HDL, hypertension, hyperglycemia, and hypertriglyceridemia. While the identification of metabolic syndrome as a clinical entity is largely accepted, some debate remains as to the threshold that must be reached for each of these factors to achieve a diagnosis of metabolic syndrome. For example National Education Program Third Adult Treatment Panel Guide (NCEP) requires that patients meet at least 3 of the following criteria: abdominal obesity (waist circumference of >88 cm for women and greater than 102 cm for men), hypertriglycermia (greater than 150 mg/dL), low HDL cholesterol (less than 40 mg/dL for men and less than 50 mg/dL for women), high blood pressure (systolic greater than 130 mm Hg, diastolic greater than 85 mm Hg), high fasting glucose (greater than 110 mg/dL). Again, it is important to point out that metabolic syndrome is a pre-diabetic state, which identifies that deleterious changes in metabolism can occur independent of the existence of diabetes (Fig 1). While understanding the effects of diabetes on the brain is important, and has received the largest amount of attention to date, it is equally important to understand the effects of the pre-diabetic state and presence of metabolic syndrome on brain homeostasis. This is based on the fact that a significant percentage of individuals will not progress to diabetes, and will potentially exist in a pre-diabetic state for decades. Additionally, understanding the earliest alterations in brain homeostasis that occur following metabolic dysfunction (non-diabetes or pre-diabetes), may allow for understanding how specific metabolic disturbances contribute to the more advanced and pathogenic alterations in brain homeostasis.

2. Metabolic dysfunction and effects on brain physiology

As part of normal brain function the brain is required to acquire, process, store, and retrieve large amounts of information. Each of these functions can be placed into different functional categories including working memory (short term), implicit memory (task associated), and declarative memory (recall of facts and events). As the result of a variety of stressors the function and performance of the brain can become impaired and ultimately result in dementia. Considerable clinical evidence suggests that a western diet, and the presence of metabolic dysfunction (pre-diabetic or metabolic syndrome), are sufficient to promote the development of cognitive disturbances and even dementia. For example, three separate studies (Health Aging and Body Composition Study, Sacramento Area Latino Study of Aging (SALSA), Longitudinal Aging Study Amsterdam) have demonstrated a significant and inverse correlation between the presence of metabolic syndrome and a longitudinal decline in cognitive performance [12–16]. Importantly, cognitive decline in these studies was determined using a number of established cognitive assessments including the mini mental status exam, delayed word-list recall, and coding tasks. Additionally, one recent longitudinal study demonstrated that obesity increased the risk for dementia (74%), even after adjusting for diabetes and cardiovascular disease [17]. Similarly studies identified that abdominal adipocity in the elderly increased the incidence of dementia even after correcting for age [18]. Also, non-elderly obese individuals have been demonstrated to have more severe brain atrophy as compared to non-obese individuals of the same age [19]. Together, these data clearly link diet-induced metabolic disturbances to the development of a number of cognitive disturbances and dementia.

A critical feature of the aforementioned clinical studies is that they each also identified that the cognitive decline in aged individuals with metabolic syndrome were much more affected than non-aged individuals, and that in every study there was a significant and inverse correlation between the level of cognitive performance and the presence of peripheral indices of inflammation. These inflammatory markers included elevated circulating levels of C-reactive peptide, alpha-1-antichymotrypsin, and interleukin-6. Although each of these previously mentioned studies examined the relationship between cognition in non-diabetics, data from the Framingham study has also demonstrated a link between type 2 diabetes and lower cognition scores [20].

The aforementioned data from population and epidemiological based studies are further supported from a number of rodent studies that link diet-induced metabolic dysfunction to the development of cognitive abnormalities. For example diet induced obesity in rodents is sufficient to promote cognitive disturbances in aging and young rodents [21–25]. Interestingly, rodent studies have demonstrated a potential role for glucocorticoids, hypertriglyceridemia, and oxidative stress in promoting brain disturbances in some rodent models of obesity [26].

It is important to point out that the majority of studies on aging and dietary effects on the brain have centered on understanding how long term type 2 diabetes mellitus influences brain function. Additionally, rodent studies have primarily focused on taking young rodents and placing them on long term diets, and maintaining them on such diets whereby animals age with the long term complications associated from having diabetes. These studies, while informative, do not provide important insight as to how a long term and persistent state of pre-diabetes or metabolic syndrome affect brain homeostasis. Additionally, previous studies are not generally designed to understand how aging may influence the ability of a western diet, and/or the presence of prediabetic state/metabolic syndrome state, to promote brain disturbances. Based on epidemiological studies and experimental evidence in rodents it is highly likely that independent of diabetes, the presence of western diet-induced metabolic

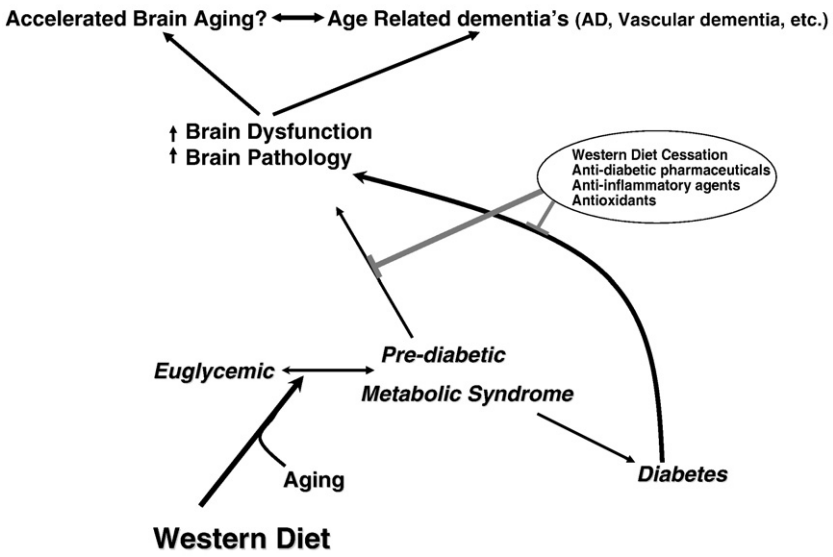

Fig. 2. Diet-induced increases in brain dysfunction and brain pathology. Consumption of a western diet is sufficient to promote metabolic dysfunction that can then lead to the development of brain pathology and cognitive disturbances. Aging likely promotes the ability of a western diet to promote metabolic dysfunction, and deleterious effects on the brain, while several clinically relevant interventions (western diet cessation, antioxidants, anti-inflammatory, anti-diabetics) likely ameliorate the effects of a western diet on metabolism and the brain.

disturbances is sufficient to induce cognitive disturbances and neuropathology that can be considered a form of accelerated aging (Fig 2). It is important to point out that there remains a tremendous void in our understanding as to which neurochemical and/or neuropathological criteria are responsible for mediating the aforementioned described disturbances in cognition (see below). It is likely that aging itself is sufficient to further accelerate the effects of a western diet and diet-induced metabolic dysfunction on the brain (Fig 2). Together, these concepts have important implications for understanding what neurological disturbances are expected to occur within the large swath of the population regularly consuming a high fat western diet in the United States.

3. Metabolic dysfunction and effects on brain pathology

It is presumed that brain pathology serves as a substrate for declines in brain performance and ultimately to the development of dementia. However, the mechanism(s) by which pathology contributes to cognitive disturbances is not linear and is clearly complex [27,28], likely relying on not only the amount of overall pathology but also taking into account the ability of the brain to adapt or respond to the presence of pathology. Regardless, a number of pathologies occur as part of normal brain aging and age-related diseases of the brain [27,28]. Key age-related pathologies include the development of proteinateous aggregates/inclusions (neurofibrillary tangles, Lewy Bodies, lipofuscin ceroid, extracellular beta amyloid deposits) and neurochemical alterations (altered trophic factor support, oxidative stress, mitochondrial abnormalities). In addition to these manifestations studies have identified a number of vascular abnormalities which appear to be pathological features of brain aging and age-related diseases of the nervous system. The potential for each of these factors contributing to cognitive disturbances following consumption of a western diet is discussed in more detail below.

3.1. Metabolic disturbances and the development of protein aggregates

While some studies have demonstrated a link between the presence of diabetes, and the presence of cognitive deterioration and neuropathology, several controversial aspects remain to be elucidated. For example, most neuropathological studies in humans have demonstrated that there is no positive correlation between the presence of diabetes and the presence of AD related pathology [28,29]. Such a discrepancy may arise as the result of the exclusion criteria used in these and other neuropathological studies, as well as the fact that most studies do not take into account the duration or severity of diabetes in the subjects analyzed. Surprisingly, at the present time there appears to be no current publications demonstrating the ability of pre-diabetic state or metabolic syndrome to modulate AD related pathology. However, it is again worth noting that studies have demonstrated a link between metabolic syndrome and the clinical diagnosis of AD dementia [30]. Studies examining the pathology in prediabetic individuals and individuals with metabolic syndrome are essential to begin to understand the reciprocal relationship between diet-induced metabolic dysfunction and the promotion of brain pathogenesis. On a similar note, there is nothing known with regard to the ability of a pre-diabetic state to modulate the presence of several well established protein-based pathologies in the brain such as neurofibrillary tangles, Lewy bodies, or lipofuscin-ceroid. Rodent studies have demonstrated the ability of a high fat and high-sucrose diet to promote the development of extracellular beta amyloid deposits [28,29,31–34], although as stated above, there does not appear to be a strong body of evidence supporting the ability of diabetes or diet-induced metabolic dysfunction to increase the burden of beta amyloid deposition in the human brain.

Given the large amount of studies in both rodents and humans that demonstrate the ability of diet-induced metabolic dysfunction to promote cognitive disturbances and dementia [30,35–40], with a corresponding lack of studies showing increased levels of neuropathology in the brain, these data raise the possibility that diet-induced cognitive disturbances are not mediated by some of the most established and well characterized forms of protein/peptide-based pathologies (beta amyloid deposition, neurofibrillary tangles, Lewy bodies, lipofuscin-ceroid). Additionally, such data may highlight the potential for other neurochemical and neuropathological features potentially serving as mediators of diet-induced cognitive disturbances. Below we discuss the potential for altered trophic factor support, mitochondrial abnormalities, and/or oxidative stress serving as key mediators of diet-induced disturbances of the brain.

3.2. Metabolic disturbances and development of altered trophic factor support

A growing body of literature has demonstrated the ability of a high fat diet and diabetes to alter the level of trophic factors [41–45]. In particular both diabetes and high fat diets have been demonstrated to alter the level of essential trophic factors such as brain derived neurotrophic factor (BDNF), raising the possibility of high-fat diets promoting brain disturbances via altering the levels of neuroprotective molecules such as BDNF [41–45]. Such changes in neurotrophic factor signaling would be expected to promote deleterious changes in signal transduction pathways, given that neurotrophic factors promote MAPK and CREB signaling, which are both necessary for neuronal homeostasis [41–44]. It is interesting to also note the strong link between decreased circulating levels of neurotrophic factors and depression [43], with metabolic dysfunction potentially contributing to depression in aging and age-related diseases via altering the circulating levels of key trophic factors [43].

3.3. Metabolic disturbances and development of mitochondrial abnormalities

Diet-induced metabolic disturbances, independent of diabetes, are associated with decreased expression of genes involved in oxidative phosphorylation and decreased expression of genes involved in mitochondria biogenesis [46–48]. These studies are coupled to additional reports demonstrating that reduced mitochondrial biogenesis occurs in response to a high fat diet as well as during diabetes [49–51]. In addition to producing fewer mitochondria via reduced biogenesis, studies have reported on the ability of high-fat diet consumption to decrease the levels of complex 1 activity within mitochondria [46]. Together, these data demonstrate the ability of high-fat western diets to rapidly promote pronounced effects on the function of mitochondria, with efficient mitochondrial function essential to brain homeostasis. A central focus of much brain aging and age-related neurodegeneration research is centered on understanding and preventing deleterious changes in mitochondrial homeostasis within the brain [28,52,53]. At present it is unclear if brain mitochondria respond similarly as muscle or liver mitochondria, in response to consumption of a high-fat western diet. If brain mitochondria, particularly mitochondria within the synapse, undergo altered biogenesis and function in response to a western diet it would open the door for novel mechanisms by which peripheral metabolic disturbances promote deleterious changes in the metabolic capacity of the brain.

Decreased levels of mitochondrial biogenesis and mitochondrial function promote an increase in fatty acid oxidation, as an alternative source for ATP generation [46,47]. However, long term upregulation of fatty oxidation in tissues such as the muscle or liver (and likely the brain), would be expected to have adverse effects on cellular homeostasis. Such deleterious outcomes from chronic elevations in fatty oxidation include elevated levels of oxidative stress and ultimately insufficient genesis of ATP. Again, it is important to note that our understanding of western diet-induced effects mitochondrial abnormalities have centered on non-CNS tissues, but may also occur in tissues such as the brain, and thus may have important implications for the development of dysfunction and pathology of the brain.

3.4. Metabolic dysfunction and increased oxidative stress

Recent studies indicate that oxidative stress may be the earliest step in western diet-induced pathogenesis [54], and may be one of the earliest and most important steps in the development of insulin resistance. Oxidative stress occurs when oxidative modifications to different cellular components causes cells to undergo deleterious changes in homeostasis due to an inability to repair or replace the macromolecules possessing oxidative damage, or as the result of insufficient synthesis of protective macromolecules to counteract the deleterious effects of oxidative damage [55–57]. Reactive oxygen species (ROS) are formed as the byproduct of many physiological processes, and can arise from both enzymatic as well as non-enzymatic sources. Well established ROS include superoxide anion, hydroxyl radical, singlet oxygen, and hydrogen peroxide. Each of these ROS is extremely unstable (and therefore reactive) due to the fact they contain an unpaired electron which causes them to rapidly interact with proteins, nucleic acids, and lipids.

There are many modes of protein oxidation which include metal catalyzed oxidation, amino acid oxidation, oxidation induced cleavage, and the conjugation of lipid oxidation products [55]. ROS mediated cleavage of peptide bonds occurs principally via the diamide pathway and the alpha-amidation pathway. Both cysteine and methionine residues can interact with ROS resulting in the production of sulfoxide, sulfenic acids, and disulfide bridges. By far the most characterized and studied oxidative modification to proteins is the protein carbonyl. The most well studies lipid oxidation-protein conjugate are the adducts mediated by the lipid peroxidation product (4-hydroxynonenal).

In addition to the oxidation of proteins, lipid peroxidation can contribute to the development of oxidative stress. A wide variety of lipid peroxidation products have been identified and demonstrated to mediate varying degrees of toxicity in the brain and other tissues [58]. The best characterized of the lipid peroxidation products is 4-hydroxynonenal (HNE) which is capable of altering cellular homeostasis via the aforementioned adduct formation and protein cross-linking [58]. Studies have identified a role for HNE and other lipid peroxidation in normal brain aging as well as a variety of age-related neurodegenerative disorders [58–63]. Lastly, the oxidation of nucleic acids is capable of promoting oxidative stress in a variety of tissues including the brain [28,57–61]. Oxidation of DNA is the best characterized but studies have also identified that oxidation of RNA may serve as a more sensitive marker of oxidative stress in the brain.

Increased levels of oxidative stress are evident in experimental models of western diet-induced metabolic dysfunction as well as samples from humans with diet-induced metabolic dysfunction [2,15,54,61,64–68]. For example studies of tissues following western diet consumption have demonstrated evidence for increased levels of oxidative damage to nucleic acids, proteins, and lipids [54,64–68]. Taken together, these data suggest that the dysfunction of tissues following western diet consumption may be due to the adverse effects of oxidative stress.

While there is significant evidence for oxidative stress potentially contributing to the pathogenesis associated with western diet consumption, several critical issues remain to be experimentally elucidated. For example, at present it remains unclear as to which cell types and brain regions are most vulnerable to the deleterious effects of western diet-induced oxidative stress. Additionally, it is unclear whether aging potentially exacerbates the ability of a western diet to induce oxidative stress in these same cell types and brain regions. Defining these aspects of western diet-mediated changes in brain homeostasis will allow us to begin to critically understand how the brain is affected by western diet consumption. Similarly, understanding the relative susceptibility of the cerebral cortex and hippocampus to undergo elevations in oxidative stress, relative to the hypothalamus, will have important implications for understanding the potential contribution of western diet-induced oxidative stress to subsequent neurobehavioral disturbances. Lastly, studies are needed to define which forms of oxidative stress (protein, lipid, nucleic acid oxidation) are most important to the development of western diet-induced disturbances in cognition. When such data is available investigators will be able to define the molecular and cellular basis by which oxidative stress potentially contributes to brain dysfunction in the adult and aged brain. Such data have tremendous implications for not only normal brain aging, but also understanding

how western diet-induced increases in oxidative stress potentially contribute to the development of a wide variety of age-related dementias including AD.

4. Future areas of research

As pointed out above, we currently know very little with regard to exactly how dietary factors (such as a high fat western diet) modulate brain homeostasis during the aging of the brain. It is clear that there are clinical and rodent studies which strongly link diet-induced metabolic disturbances (in absence of diabetes) to the development of dementia. The progressive nature by which western diet consumption promotes brain disturbances raises the possibility that by studying this model we will be better able to not only understand the linkages between metabolism and the brain, but also begin to understand the complex relationship between brain pathology and altered brain function.

It remains unclear as to which peripheral pathologies that are associated with a western diet, are also observed in the brain. Identifying the similarities and temporal profiles of these brain changes, as related to peripheral tissues, may allow for mechanistic insight as to how high fat western diets disrupt brain homeostasis. One key aspect to investigate in the future will be to elucidate whether western diet consumption potentially mediates brain disturbances via reducing the ability of the brain to successfully respond to stressors (as is observed in other tissues). A decreased capacity to repair or replace damaged brain systems may play a causal role in promoting both neuropathology and neurobehavioral deficits. For example, decreased trophic support or vascular support in response to a western diet (as reported in non-CNS tissues) would be expected to potentially contribute to the development of neuropathology and dementia.

In speculating for this portion of the manuscript the authors are particularly excited about the potential that we might be able to gain mechanistic insight to the "sundowning" which is observed in the elderly and individuals with dementia. "Sundowning" occurs when there is increased confusion and cognitive disturbances in these individuals in later stages of the day [69]. While most studies have focused on the potential contribution of fatigue, low lighting, and changes in home environment as triggers to sundowning one can also envision a role for metabolic disturbances contributing to sundowning. Metabolic disturbances, which likely can be successfully modulated using pharmaceutical or nutritional interventions, may play a key role in reducing or delaying sundowning. Additionally, sundowning may be another key experimental model for understanding how pathology (aging, age-related neurodegenerative conditions) contribute to subsequent cognitive disturbances. Increasing the amount of "good days", or high level of cognitive function within a given day in demented individuals, will likely be a key area to target with future dementia research.

The findings discussed in this review have demonstrated a role for diet-induced disturbances in metabolism (in the absence of diabetes) to serve as mediators of neuropathology and dementia. These data highlight the potential for using diet-based studies as a means of understanding the relationship between pathology and dementia, and the reciprocal relationship of individual pathologies and neurochemical disturbances to one another. The fact that in the pre-diabetic state the effects of a western diet are partially or even fully reversible raises a tremendous opportunity for the development of potential therapeutic interventions. Such therapies may be either behavioral (cessation of western diet and increased exercise), or pharmacological based (Fig 2), and considerable research is needed to understand the efficacy of such interventions towards western diet-induced effects on the brain.

Certainly the concept of linking diet-induced metabolic dysfunction to brain pathogenesis and dementia is not a new concept, for example in 1996 Smith et al postulated a linking between diabetes and Alzheimer's disease based on the common link of increased levels of advanced glycation end products (AGE) in each of these disorders [70]. Additionally, work from the Smith and Perry group went on to outline the ability of AGE to mediate many aspects of Alzheimer's disease pathogenesis [71,72], suggesting an active role for AGE's in Alzheimer's. What this review focuses on is the novel concept that a pre-diabetic state (independent of diabetes) is likely sufficient to accelerate many aspects of brain aging including increased levels of dementia and brain pathogenesis. This has important implications for the 71 million pre-diabetic individuals in the United States who are all aging, and a vast majority of which will never go on to develop diabetes. We propose that these individuals will likely have an increased propensity for age-related dementia's, and will likely exhibit accelerated brain aging on both a pathological as well and neurophysiological level. Understanding the effects of a pre-diabetic on the aging brain, and understanding what effects can be reversed by routinely prescribed interventions is a critical area of future research. Taken together, these finding highlight the importance of continuing research on this exciting area of research, which has not only tremendous implications for our understanding of the brain and the genesis of brain disease, but also for our understanding of how the daily choices in our diet lays the groundwork for the development or prevention of brain disease.

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